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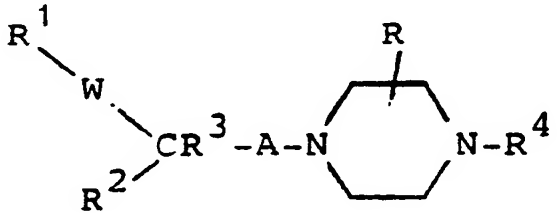
(54) Title: PIPERAZINE DERIVATIVES



(I)

(57) Abstract

Compounds of formula (I) and their pharmaceutically acceptable acid addition salts, wherein W is $(CH_2)_m$, CHOH or O, m is one of the integers 1 or 2, A is an alkylene chain of 1 to 3 carbon atoms optionally substituted by one or more (lower)alkyl groups, R is hydrogen or lower alkyl, $R^1$ and $R^2$ are each, independently, aryl or heteroaryl radicals with the proviso that $R^1$ is not an optionally substituted indolyl radical, $R^3$ is hydrogen or lower alkyl and $R^4$ is an aryl or heteroaryl radical, are $5\text{-}HT_{1A}$ binding agents which may be used, for example, in the treatment of CNS disorders such as anxiety.

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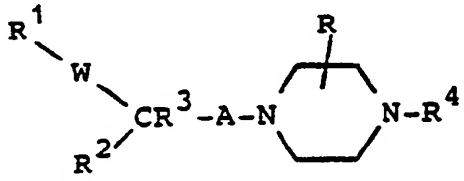
# PIPERAZINE DERIVATIVES

This invention relates to piperazine derivatives, to processes for their preparation, to their use and to pharmaceutical compositions containing them. The novel compounds act upon the central nervous system by binding to 5-HT receptors (as more fully explained below) and hence can be used as medicaments for treating human and other mammals.

The novel compounds of the invention are those of the general formula



(I)

and the pharmaceutically acceptable acid addition salts thereof.

In formula (I):
W is $(CH_2)_m$, CHOH or O,
m is one of the integers 1 or 2,
A is an alkylene chain of 1 to 3 carbon atoms optionally substituted by one or more (lower)alkyl groups,
R is hydrogen or lower alkyl,
$R^1$ and $R^2$ are each, independently, aryl or heteroaryl radicals with the proviso that $R^1$ is not an optionally substituted indolyl radical.
$R^3$ is hydrogen or lower alkyl and
$R^4$ is an aryl or heteroaryl radical.

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. Preferably such radicals contain 1 to 4 carbon atoms. Examples of

"lower alkyl" radicals are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and isopentyl.

When used herein "aryl" means an aromatic radical having 6 to 12 carbon atoms (e.g. phenyl or naphthyl) which optionally may be substituted by one or more substituents. For example, when $R^1$ or $R^2$ is aryl it may be a phenyl or naphthyl radical optionally substituted by one or more lower alkyl, lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, cyclopropylmethoxy), halogen, halo(lower)alkyl (e.g. trifluoromethyl), nitro, amino, (lower)alkylamino, di(lower)alkylamino, phenyl, halophenyl, (lower)alkyl phenyl or (lower)alkoxy phenyl substituents. When $R^4$ is aryl it may be, for example, a phenyl or naphthyl radical optionally substituted by one or more of the substituents listed above and/or by one or more hydroxy, hydroxy(lower)alkyl (e.g. hydroxymethyl), $-CONR^5R^6$ (where $R^5$ and $R^6$ are each hydrogen or lower alkyl) or $-NHSO_2$(lower)alkyl substituents. Preferably the aryl radical $R^4$ contains a substituent (e.g. lower alkoxy) in the ortho position. A particularly preferred example of $R^4$ is o-(lower)alkoxyphenyl (e.g. o-methoxyphenyl).

The term 'heteroaryl' refers to a mono or bicyclic aromatic radical containing one or more hetero ring atoms (e.g. oxygen, nitrogen, sulphur) and which may be optionally substituted by one or more substituents. Preferred examples of substituents for the heteroaryl radicals $R^1$ and $R^2$ are given above for the aryl radicals $R^1$ and $R^2$ while preferred examples of substituents for the heteroaryl radical $R^4$ are given above for the aryl radical $R^4$. The heteroaryl radical may for example contain up to 11 ring atoms.

Preferably the heteroaryl radical is a monocyclic radical containing 5 to 7 ring atoms or a bicyclic radical containing 8 to 11 ring atoms. Preferably the hetero ring contains a nitrogen hetero atom with or without further hetero atoms. Examples of heteroaryl groups $R^1$ and $R^2$ are optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl. These groups may be connected to the remainder of the molecule via a ring heteroatom or a ring C atom.

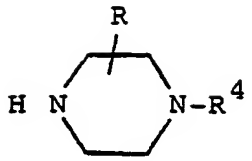
Examples of the heteroaryl group $R^4$ include optionally substituted pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl or isoquinolinyl.

Preferred compounds have the following substituents either independently or in combination:-

(a) W is $CH_2$, CHOH or -O-
(b) A is $-CH_2-$
(c) $R^1$ is aryl, preferably phenyl or substituted phenyl
(d) $R^2$ is phenyl or pyridyl
(e) $R^3$ is hydrogen
(f) $R^4$ is aryl
(g) R is hydrogen

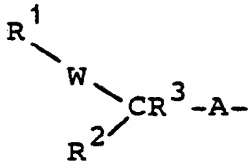
The compounds of the invention may be prepared by methods known in the art from known starting materials or starting materials that may be prepared by conventional methods.

One method of preparing the compounds of the invention comprises alkylating a piperazine derivative of formula



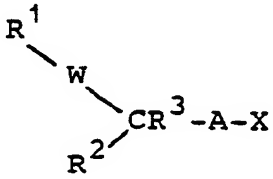
(II)

with an alkylating agent providing the group



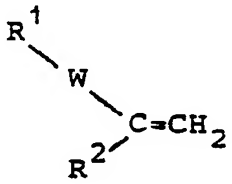
(III)

The alkylating agent may be, for example, a compound of formula



(IV)

where $R^1$, $R^2$, $R^3$, W and A are as defined above and X is a leaving group such as halogen or an alkyl- or aryl-sulphonyloxy group. Alternatively the alkylating agent may be an unsaturated compound of formula

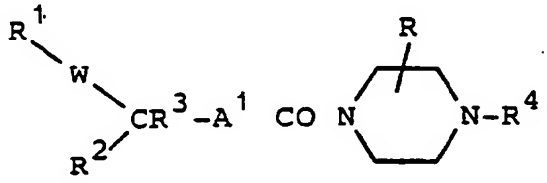


(V)

(where W is $(CH_2)_m$ or O and $R^2$ is an electron withdrawing group e.g. an optionally substituted 2- or 4- pyridyl, 2- or 4- pyrimidyl or 2- pyrazinyl group) and the compound of formula (V) is reacted with the

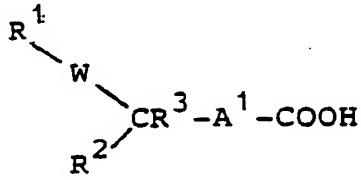
piperazine compound of formula (II) by means of a Michael reaction.

The compounds of formula (I) may also be prepared by reduction of an amide of formula



(VI)

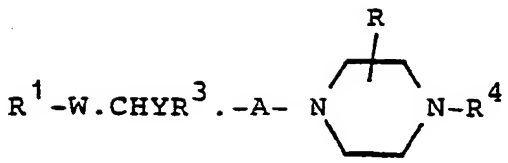
where R, $R^1$, $R^2$, $R^3$, $R^4$ and W are as defined above and $A^1$ is an alkylene radical of 1 or 2 carbon atoms optionally substituted by one or more (lower)alkyl groups. The reduction may, for example, be carried out with a hydride transfer agent e.g. borane-dimethylsulphide or lithium aluminium hydride. The starting amide of formula (VI) may be made by acylating a piperazine derivative of formula (II) above with an acylating derivative of an acid of formula



(VII)

The acylating derivative may be, for example, the acid chloride.

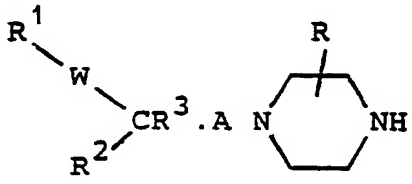
Compounds of the invention in which $R^2$ is a heteroaryl group attached via a ring N-atom may be prepared by reacting a heteroaromatic compound of formula $R^2H$ e.g. imidazole with, a compound of formula



(VIII)

where R, $R^1$, $R^3$, $R^4$ and A are as defined above, W is $(CH_2)_m$ or O and Y is a leaving group such as halogen or an alkyl- or aryl- sulphonyloxy group.

An alternative method of preparing the compounds of the invention comprises arylating or heteroarylating a compound of formula

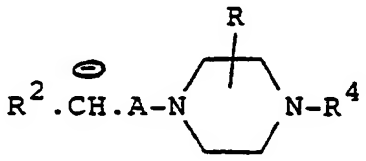


(IX)

where A, R, $R^1$ and $R^2$ are as defined above, W is $(CH_2)_m$ or O and $R^3$ is lower alkyl.

For example the compound of formula (IX) may be reacted with a fluorobenzene compound which is substituted by an electron withdrawing group (e.g. -CHO, cyano, nitro).

Another method of preparing the compounds of the invention comprises reacting a compound having the anion



(X)

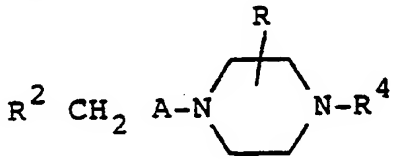
with a compound of formula

$$R^1CHO \qquad (XIa)$$

or

$$R^1(CH_2)_mY \qquad (XIb)$$

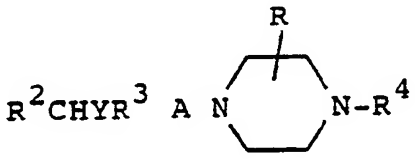
where $R^1$ and m are as defined above and Y is a leaving group such as halogen. Reaction of the aldehyde (XIa) with the anion gives a compound of the invention in which W is CHOH while reaction of the compound (XIb) with the anion gives a compound of the invention in which W is $(CH_2)_m$. The anion (X) may be prepared by known methods. For example when $R^2$ is an electron withdrawing heteroaryl radical the anion may be prepared by reacting the compound



(XII)

with a base e.g. n-butyl lithium.

Compounds of the invention in which W is O may be prepared by reacting a compound having the anion of formula $R^1O^-$ (for example a compound of formula $R^1O\ M$ where M is an alkali metal) with a compound of formula



(XIII)

where A, R, $R^2$, $R^3$ and $R^4$ are as defined above, and Y is a leaving group such as halogen or an alkyl- or aryl-sulphonyloxy group.

Compounds of the invention in which W is $CH_2$ or CHOH

may be prepared by reduction of a compound of formula (I) in which W is CO.

Compounds of the invention in which $R^3$ is lower alkyl may be prepared by reacting a compound of the invention in which $R^3$ is hydrogen with a strong base (eg butyllithium) and with an alkylating agent (eg iodomethane).

If in any of the other processes mentioned herein, a substituent on the group $R^4$ or on the group $R^1$ and/or $R^2$ is other than the one required the substituent may be converted to the desired substituent by known methods. For example, a -CHO substituent may be reduced to hydroxymethyl, a nitro group may be reduced to a amino group which may be sulphonated to give a $-NHSO_2$(lower)alkyl substituent, a cyano group may be hydrolysed to an acid which may be esterified or converted to an amide.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric,

hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic, p-toluenesulphonic, oxalic and succinic acids.

The compounds of the invention contain an asymmetric carbon atom, so that the compounds can exist in different steroisomeric forms. The compounds can be for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

The compounds of the present invention possess pharmacological activity. In particular, they act on the central nervous system by binding to 5-HT receptors. In pharmacological testing it has been shown that the compounds particularly bind to receptors of the 5-$HT_{1A}$ type. In general, the compounds selectively bind to receptors of the 5-$HT_{1A}$ type. Many exhibit activity as 5-$HT_{1A}$ antagonists in pharmacological testing. The pharmacological testing of the compounds indicates that they can be used for the treatment of neuro-psychiatric disorders, such as anxiety and depression in mammals, particularly humans. They may also be useful as hypotensives and as agents for regulating the sleep/wake cycle, feeding behaviour and/or sexual function.

The compounds of the invention are tested for 5-$HT_{1A}$ receptor binding activity in rat hippocampal membrane homogenate by the method of B S Alexander and M D Wood, J Pharm Pharmacol, 1988, 40, 888-891. 1-(2-Methoxyphenyl)-4-[2-((α-hydroxybenzyl)-2-pyridyl) ethyl]piperazine, a representative compound of the invention, had an $IC_{50}$ of 20nM in this procedure.

The compounds are tested for 5-$HT_{1A}$ receptor antagonism activity in a test involving the antagonism of 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH DPAT) syndrome in the rat.

The invention also provides a pharmaceutical composition comprising a compound or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid or liquid.

Solid form compositions include powders, granules, tablets, capsules (e.g. hard and soft gelatine capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aides, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, e.g. from 0.03 to 99%. preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweetners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution, alcohols, e.g. glycerol and glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it

can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged composition, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquid. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compostions in package form. The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient.

The following Examples illustrate the invention:

Example 1

1-(2-Methoxyphenyl)-4-[2-((α-hydroxy-2-methoxybenzyl)-2-pyridyl)ethyl]piperazine

n-Butyl-lithium (1.6M solution in hexane) (7.0 ml, 11.2 mmol, 1.1 equiv.) was added dropwise at below -60°C to a solution of 1-(2-methoxyphenyl)-4-(2-pyridylethyl)piperazine base (3.00 g, 10.1 mmol) in anhydrous THF (20 ml). The resulting orange-red solution was stirred for a further 0.25 h at -70°C then quenched with a solution of ortho-anisaldehyde (1.5 g, 11.0 mmol) in anhydrous THF (2 ml). The reaction mixture was poured into water (50 ml) and extracted with dichloromethane (2 x 75 ml). The organic extract was washed (brine), dried ($Na_2SO_4$) and concentrated in vacuo. The residue was subjected to chromatography ($SiO_2$: $Et_2O$) to give the first $R_f$ diastereoisomer as a white foam which was dissolved in isopropanol (20 ml) and acidified with ethanolic hydrogen chloride to afford the first diastereoisomer of the title compound as the trihydrochloride (227 mg), m.p. 140-145°C (Found: C,57.7;H,6.5;N,7.8 $C_{26}H_{31}N_3O_3.3HCl$ requires C,57.5;H,6.3;N,7.7%).

The low $R_f$ diastereoisomer was obtained from later fractions which were concentrated in vacuo to give a white foam, dissolved in isopropanol (15 ml), and acidified with ethanolic hydrogen chloride. The salt slowly crystallised to afford the second diastereoisomer of the title compound as the trihydrochloride isopropanolate (203 mg), m.p. 120-123°C (Found: C,58.1;H,7.0:N,7.3. $C_{26}H_{31}N_3O_3$ 3HCl. $C_3H_7OH$ requires C, 57.8; H,6.85;N,7.0%).

Example 2

1-(2-Methoxyphenyl)-4-[(2-((α-hydroxybenzyl)-2-pyridyl)ethyl]piperazine

n-Butyl-lithium (1.6M solution in hexane) (2.2 ml, 3.5 mmol, 1.04 equiv.) was added dropwise at below -65°C to a solution of 1-(2-methoxyphenyl)-4-(2-pyridylethyl) piperazine (1.00 g, 3.36 mmol) in anhydrous THF (15 ml). The solution was stirred for a further 0.25 h at -70°C then quenched with a solution of benzaldehyde (0.36 g, 3.39 mmol) in anhydrous THF (2 ml). The reaction mixture was poured into water (25 ml) and extracted with dichloromethane (50 ml). The organic extract was washed (brine), dried ($Na_2SO_4$), and concentrated in vacuo to afford an orange-yellow oil (1.1 g). This was subjected to chromatography ($SiO_2$: $Et_2O$) to give the title compound dihydrochloride, three-quarter hydrate (0.81 g) as a 55:45 mixture of diastereoisomers, m.p. 117-121°C (Found: C,61.3;H,6.7;N,8.55. $C_{25}H_{29}N_3O_2.2HCl.075H_2O$ requires C,61.3;H,6.7;N,8.6%).

Example 3

1-(2-Methoxyphenyl)-4-(2-phenoxy-2-phenylethyl)-piperazine

(a) 1-(2-Methoxyphenyl)piperazine hydrochloride (9.15 g; 0.04 m) suspended in methylene chloride (150 ml) was treated with diisopropylamine (14 ml) to give a clear solution α-Chlorophenylacetylchloride (6.32 ml; 0.04 m) in methylene chloride (20 ml) was added to the

ice cold solution of amines over 20 minutes. The mixture was stirred cold for a further 45 mins, then at ambient temperature for 4 hrs. The solution was washed well with water and dried over $MgSO_4$. The residue of 1-(2-methoxyphenyl)-4-(1-oxo-2-chloro-2-phenylethyl piperazine on evaporation was a light brown oil that became a glass on standing.

(b) Sodium hydride 80% dispersion in oil (1.7 g) was added to dry DMF (100 ml) under argon. Phenol (3.76 g; 0.04 m) was added over 20 mins and the resulting grey mixture was stirred a further 20 mins and cooled to 0°C. A solution of 1-(2-methoxyphenyl)-4-(1-oxo-2-chloro-2-phenylethyl)piperazine (13.8 g; 0.04 m) in dry DMF (60 ml) was added over 20 mins. The mixture was heated to 60°C over a period of about 3 hrs and then maintained at 60° C for 2½ hrs and then stirred at ambient temperature overnight. The mix was cooled to 0°C, treated with 10 ml crushed ice and the DMF was vacuumed off. The residue, in methylene chloride, was washed well with water and dried over magnesium sulphate. The oil resulting on evaporation, solidified on standing for a few days to give 1-(2-methoxyphenyl)-4-(1-oxo-2-phenoxy-2-phenylethyl) piperazine.

(c) 1-(2-Methoxyphenyl)-4-(1-oxo-2-phenoxy-2-phenylethyl)piperazine (3.77 g; 0.1 m) in dry THF (30 ml) was added to lithium aluminium hydride (1.5 g) in cold THF (100 ml) and the mixture refluxed for 4½ hours. After standing overnight the mixture was treated with ammonium chloride (1.56 g) in water (5 ml). The mixture was stirred for ½ hour and then filtered. The solid was washed with ethyl acetate and

the combined filtrates evaporated to give an oil that was dissolved in ethanol and acidified with ethereal hydrogen chloride to give the title compound as the dihydrochloride (2.3 g), m.p. 196-200°C (Found C, 65.0;H,6.7;N,6.0. $C_{25}H_{28}N_2O_2$ requires C, 65.1;H,6.55; N 6.1%).

## Example 4

### 1-(2-Methoxyphenyl-4-[2-(3-methylphenoxy)-2-phenylethyl]piperazine

The title compound was obtained following the procedure of Example 3(c) by reduction of 1-2(methoxyphenyl-4-[1-oxo-2-(3-methylphenoxy)-2-phenylethyl]piperazine which was prepared in a manner analogous to that of Example 3(a) and (b). The product was obtained as the dihydrochloride, half hydrate, m.p. 186-189°C.

## Example 5

### 1-(2-Methoxyphenyl)-4-[(2-(4-fluorobenzyl)-2-pyridyl)ethyl]piperazine

n-Butyllithium (1.6M solution in hexane) (9.00 ml, 14.4 mmol) was added dropwise at -70°C to a solution of 1-(2-methoxyphenyl)-4-(2-(4-pyridyl)ethylpiperazine (4.010 g, 13.48 mmol) in anhydrous THF (40 ml). The

solution was stirred for 0.25 h at -70°C then treated dropwise with a solution of 4-fluorobenzyl chloride (2.10 g, 14.52 mmol) in THF (10 ml) at below -50°C. The mixture rapidly decolourised and was allowed to warm to 0°C, quenched with water (20 ml), and extracted with dichloromethane (1 x 75 ml, 2 x 25 ml). The extract was washed (brine; 20 ml), dried ($Na_2SO_4$), and concentrated in vacuo to give a brown oil (5.6 g). This was subjected to chromatography ($SiO_2$ : $Et_2O$) to afford the product as a very pale yellow oil (4.23 g).

A sample of the base (1.535 g) was dissolved in ether (30 ml), acidified with ethereal hydrogen chloride, and concentrated in vacuo to give a white solid. This was recrystallised from EtOH - EtOAC to afford the title compound as the dihydrochloride dihydrate, m.p. 133-136°C. (Found: C,58.67; H,6.69; N,8.12. $C_{25}H_{28}FN_3O.2HCl.2H_2O$ requires C,58.37; H,6.66; N,8.17%).

## Example 6

### 1-(2-Methoxyphenyl)-4-[(2-(4-fluorobenzyl)-2-methyl-2-(2-pyridyl)ethyl]piperazine

A solution of n-butyllithium (9ml, 1.6M solution in hexane) was added dropwise to a solution of 1-(2-methoxyphenyl)-4-[2-(2-pyridyl)ethyl]piperazine (4.05 g, 13.6 mmol) in dry THF (80 ml) maintained at -70°C. After addition the solution was maintained at -70°C for a further 0.5 h and then a solution of 4-fluorobenzyl chloride (1.96 g, 13.6 mmol) in dry THF (20 ml) added at the same temperature. After stirring at -70°C for 0.25 h a further 9ml of n-butyllithium

was added followed 0.25 h later by iodomethane (1 ml). The reaction was allowed to rise to ambient temperature, quenched with brine (25 ml) and extracted with dichloromethane. The organic phase was dried, evaporated and the residue chromatographed on silica using 1:1 hexane-ether as eluent to give the title product (1.8 g). The base was dissolved in ethanol (20 ml) and acidified with ethanolic-HCl and diluted with ether to precipitate the crystalline dihydrochloride (1.5 g), m.p. 198-200°C.

## Example 7

(a) 1-(2-Methoxyphenyl)-4-[3-(1H-imidazol-1-yl)-1-oxo-2-phenylpropyl]piperazine

Atropic acid (2.11 g, 0.014 m) suspended in dry dichloromethane (30 ml) was treated with 1,1-carbonyl diimidazole (2.31 g, 0.0142 m) over 10 minutes at ambient temperature and stirring was continued for 30 minutes. 2-Methoxyphenylpiperazine (2.76 g, 0.0143 m) was added and the mixture was stirred for 16-20 hrs. The solution was washed with water and the dichloromethane fraction was dried over magnesium sulphate. The residue was purified by dry column flash chromatography to give 1.46 g of product .

(b) 1-(2-Methoxyphenyl)-4-[3-(1H-imidazol-1-yl)-2-phenylpropyl]piperazine

The above amide from part (a) (4.9 g, 0.0125 m) was reduced in tetrahydrofuran using 1.0 g of lithium aluminium hydride. After 1 hr at 80°C the mixture was cooled to 0-5°C and treated with (i) water (1 ml); (ii)

2N NaOH (2 ml) and (iii) water (1 ml). The filtrate from the resulting mixture was evaporated and the residue was dissolved in chloroform. The chloroform solution was washed with water and dried over magnesium sulphate to give 4.3 g of an oil that was purified by dry column flash chromatography to give 2.0 g of pure title compound base. 1.6 g of this base was dissolved in ethanol and acidified with ethanolic hydrogen chloride. The residue on evaporation was crystallised from ethanol to give 0.7 g of the trihydrochloride salt, m.p. 201-205°C.

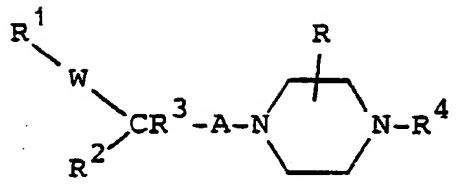
## Example 8

### 1-(2-Methoxyphenyl)-4-[2-(4-fluorobenzyl)-2-(4-pyridyl)ethyl]piperazine

1-(2-Methoxyphenyl)-4-[2-(4-pyridyl)ethyl]piperazine (5.94 g, 20 mmol) was dissolved in anhydrous THF (70 ml) and the solution cooled to about -78°C, n-Butyllithium (1.6M solution in hexane, 18 ml) was added in portions, then the mixture was stirred for 1 hour, at below -70°C. The anion was quenched with p-fluorobenzylbromide (3.18 g, 16.8 mmol) in THF (3 ml) and the mixture was warmed to room temperature when water (50 ml) was added. The organic component was extracted by dichloromethane, then washed with brine, dried using sodium sulphate and concentrated in vacuo. The resulting oil was purified by column chromatography using methanol:chloroform (0:100 - 5:95 gradient), affording the pure product. Addition of ethanolic HCl to the oil gave the title compound as the trihydrochloride 1.5 hydrate (1.25 g), m.p. 173-175°C.

## CLAIMS

1. A compound of general formula (I)



(I)

or a pharmaceutically acceptable acid addition salt thereof, wherein

W is $(CH_2)_m$, CHOH or O,
m is one of the integers 1 or 2,
A is an alkylene chain of 1 to 3 carbon atoms optionally substituted by one or more (lower)alkyl groups,
R is hydrogen or lower alkyl,
$R^1$ and $R^2$ are each, independently, aryl or heteroaryl radicals with the proviso that $R^1$ is not an optionally substituted indolyl radical,
$R^3$ is hydrogen or lower alkyl and
$R^4$ is an aryl or heteroaryl radical.

2. A compound as claimed in claim 1 wherein A is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$.

3. A compound as claimed in claim 1 or 2 wherein $R^1$ and $R^2$ are independently phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl or tetrazolyl each of which may be substituted by one or more lower alkyl, lower alkoxy, halogen, halo(lower)alkyl, nitro, amino, (lower)alkylamino, di(lower)alkylamino, phenyl,

halophenyl, (lower)alkylphenyl or (lower)alkoxyphenyl substituents.

4. A compound as claimed in any one of the preceding claims in which $R^4$ is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl or isoquinolinyl optionally substituted by one or more of the substituents defined in claim 3.

5. A compound as claimed in claim 1 which is 1-(2-methoxyphenyl)-4-[2-((α-hydroxy-2-methoxybenzyl)-2-pyridyl)ethyl]piperazine or

1-(2-methoxyphenyl)-4-[(2-((α-hydroxybenzyl)-2-pyridyl)ethyl]piperazine or

1-(2-methoxyphenyl)-4-(2-phenoxy-2-phenylethyl)-piperazine or

1-(2-methoxyphenyl-4-[2-(3-methylphenoxy)-2-phenylethyl]piperazine or

1-(2-methoxyphenyl)-4-[(2-(4-fluorobenzyl)-2-pyridyl)ethyl]piperazine or

1-(2-methoxyphenyl)-4-[(2-(4-fluorobenzyl)-2-methyl-2-(2-pyridyl)ethyl]piperazine or

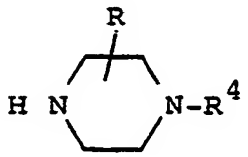
1-(2-methoxyphenyl)-4-[(3-(1H-imidazol-1-yl)-2-phenylpropyl]piperazine or

1-(2-methoxyphenyl)-4-[(2-(4-fluorobenzyl)-2-(4-pyridyl)ethyl]piperazine

or a pharmaceutically acceptable acid addition salt thereof.

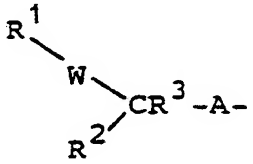
5. A process for preparing a compound claimed in claim 1 which comprises

(a) alkylating a piperazine derivative of formula



(II)

(where R and $R^4$ are as defined in claim 1) with an alkylating agent providing the group

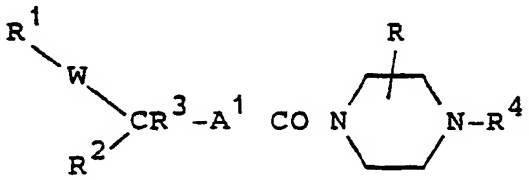


(III)

(where A, W, $R^1$, $R^2$ and $R^3$ are as defined in claim 1)

or

(b) reducing an amide of formula



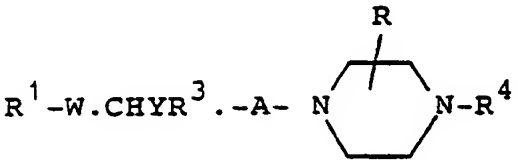
(VI)

where R, $R^1$, $R^2$, $R^3$, $R^4$ and W are as defined in claim 1 and $A^1$ is an alkylene radical of 1 or 2 carbon atoms optionally substituted by one or more (lower)alkyl

groups

or

(c) reacting a heteroaromatic compound of formula $R^2H$ (where $R^2$ is a heteroaryl group) with a compound of formula

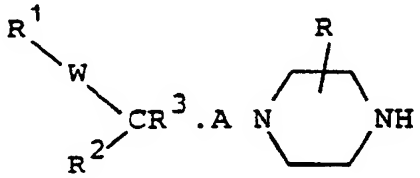


(VIII)

where R, $R^1$, $R^3$, $R^4$ and A are as defined in claim 1, W is $(CH_2)_m$ or O (where m is as defined in claim 1) and Y is a leaving group

or

(d) arylating or heteroarylating a compound of formula

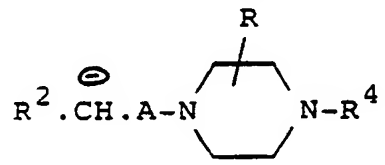


(IX)

where A, R, $R^1$ and $R^2$ are as defined in claim 1, W is $(CH_2)_m$ or O (where m is as defined in claim 1) and $R^3$ is lower alkyl

or

(e) reacting a compound having the anion



(X)

(where R, $R^2$, $R^4$ and A are as defined in claim 1) with a compound of formula

$$R^1CHO \qquad \text{(XIa)}$$

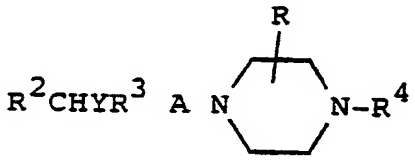
or

$$R^1(CH_2)_mY \qquad \text{(XIb)}$$

where $R^1$ and m are as defined in claim 1 and Y is a leaving group

or

(f) reacting a compound having an anion of formula $R^1O^-$ (where $R^1$ is as defined in claim 1) with a compound of formula



(XIII)

where A, R, $R^2$, $R^3$ and $R^4$ are as defined in claim 1 and Y is a leaving group

or

(g) reducing a compound of formula (I) in which W is CO to give a compound claimed in claim 1 in which W is $CH_2$ or CHOH.

or

(h) reacting a compound claimed in claim 1 in which $R^3$ is hydrogen with a strong base and with an alkylating agent to give a compound claimed in claim 1 in which $R^3$ is lower alkyl

or

(i) converting a base claimed in claim 1 into a pharmaceutically acceptable acid addition salt thereof

or

(j) converting a pharmaceutically acceptable acid addition salt claimed in claim 1 into a free base.

6. A pharmaceutical composition comprising a compound claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable carrier.

7. A process for preparing a pharmaceutical composition which comprises bringing a compound as claimed in claim 1 into association with a pharmaceutically acceptable carrier.

8. A compound as claimed in claim 1 for use as a pharmaceutical.

9. A compound as claimed in claim 1 for use as an anxiolytic, an antidepressant, a hypotensive or as an agent for regulating the sleep/wake cycle, feeding behaviour and/or sexual function.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01693

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D295/08; C07D521/00; C07D213/38; A61K31/495

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D ; A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| A | EP,A,0 382 636 (LABS. DEL DR. ESTEVE, S.A.) 16 August 1990 --- | 1 |

° Special categories of cited documents :[10]

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 19 DECEMBER 1991 | 13 JAN 1992 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | PAUWELS G.R.A. |

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# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101693 SA 51811

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/02/92
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP-A- 0382636 | 16-08-90 | FR-A- 2642758 | 10-08-90 |



For more details about this annex : see Official Journal of the European Patent Office, No. 12/82